with patients' clinical condition, and measurements are best completed while patients are on gluten-containing diets.

—Aliya Khan, MD, FRCPC, FACP
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by e-mail

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Chest pain, dyspnea, and cough

How benign is benign use of nitrofurantoin for prophylaxis of urinary tract infections (UTIs)? I have read with great interest an article by L. Nicolle and colleagues, "Uncomplicated urinary tract infection in women. Current practice and the effect of antibiotic resistance on empiric treatment."[1] The authors refer to the efficacy and safety profile of nitrofurantoin for short-term treatment of uncomplicated urinary tract infection. It is important to mention, however, that long-term treatment with nitrofurantoin can have dangerous complications.

Recently, I have seen several elderly women in the emergency department who were receiving prophylactic nitrofurantoin for recurrent UTIs. These patients have been prescribed nitrofurantoin for years, despite known warnings and adverse side effects that are well described in the nitrofurantoin monograph in the *Compendium of Pharmaceuticals and Specialties*.

Use of nitrofurantoin for longer than 6 months can lead to subacute, acute, or chronic pulmonary hypersensitivity reaction, the 2 most common forms of which are interstitial pneumonitis and pulmonary fibrosis. Patients might present with dyspnea on exertion, cough, chest pain, and malaise. Risk of lung toxicity varies among patients receiving prophylactic nitrofurantoin. A 10-year retrospective Swedish study of long-term nitrofurantoin use has demonstrated that older women are more prone to developing lung toxicity than their male counterparts or younger women.[2]

The potential irreversible side effects that are well described in the literature are not commonly considered when assessing patients in the emergency department who are receiving nitrofurantoin prophylaxis. A recent small study looked at the radiologic changes in elderly women receiving nitrofurantoin prophylaxis who presented with dyspnea, cough, and chest pain. Authors of the study concluded that the radiologic findings are relatively nonspecific on chest film and usually include bilateral areas of ground-glass opacities on computed tomography of the chest.[3]

There are several medications, chemicals, and bacteria—such as bleomycin, methotrexate, cyclophosphamide, amiodarone, procainamide, penicillamine, gold, asbestos, silica, mycobacteria, and fungi—that are well known to the medical community for their potential to induce pulmonary toxicity. However, health care providers, and especially trainees, are not well educated about potential risks related to nitrofurantoin-induced lung toxicity.

In the last decade, many immunologic mediators were shown to play a role in drug-induced lung fibrosis, such as interleukin-1, interleukin-13, tumour necrosis factor-alpha, and interferon gamma in bleomycin-induced pulmonary fibrosis.[4] Nitrofurantoin induces pulmonary hypersensitivity reactions, likely via redox cycling of the nitro group and its radical anion; this process is also known as oxidative stress.[5] Several medications have been shown to ameliorate drug-induced lung toxicity in animal models.[4] No antidote has been found in human beings, however.[5]

No randomized controlled trials have examined potential treatment strategies for nitrofurantoin-induced pulmonary inflammatory reactions. The standard clinical approach is to discontinue an offending agent and determine whether the patient requires in-hospital monitoring and supportive care. Some reports refer to steroid therapy in acute and chronic cases as being beneficial for resolution of symptoms. Fortunately, most nitrofurantoin-induced lung toxicity is reversible when the medication is discontinued.

It is very important to consider these side effects when prescribing nitrofurantoin for prophylaxis and when assessing patients who have dyspnea, chest pain, and cough and who are receiving long-term therapy with nitrofurantoin.

—Val E. Ginzburg, MSC, MD
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by e-mail

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Clarifying omega-3 fatty acid recommendations

I applaud Dr Schwalfenberg's review of omega-3 fatty acids, published in the June 2006 issue of *Canadian*

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Family Physician.[1] A recent article published in the *British Medical Journal,*[2] however, which found no decrease in mortality or cardiovascular disease with omega-3 supplementation, appears to contradict Dr Schwalfenberg's conclusions. I and others are left wondering. Comments would be appreciated.

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by e-mail

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Thank you for the great article on omega-3 fatty acids in *Canadian Family Physician.*[1] But a recent article in *Patient Care,*[2] which cited study findings that men who consumed the most alpha-linolenic acid were twice as likely to be diagnosed with advanced prostate cancer as those who consumed the least alpha-linolenic acid, was worrisome. Do you have any comments or more information regarding omega-3 (or alpha-linolenic acid) and prostate cancer?

—Nelson Daniels, MD
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by mail

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Response

First, I would like to thank Dr Biro for his valid question.

The *British Medical Journal* (*BMJ*) meta-analysis by Hooper et al[1] came to the conclusion that there is a null effect for omega-3 fatty acid supplementation. However, was it not only 2 years ago that another article in the *BMJ* said the opposite?[2]

More than 30 responses by prominent researchers have shown their concern with the recent *BMJ* article. One reviewer, Ka He, from Northwestern University, lists at least 5 reasons this review is inadequate.[1] A second reviewer stated that the DART-2 trial included in the *BMJ* meta-analysis has a number of methodologic problems and should not have been included[1] (inclusion of this trial alone made the results come out quite differently). Another reviewer stated that the *BMJ* article was a "disservice to public health."[1]

Dietary recommendations and exercise are first-line therapy for cardiovascular disease. As physicians we instruct our patients to avoid certain "bad fats" (saturated and trans fats) and cholesterol. What about providing instruction on good fats? One of the reasons I wrote my article[3] was to present dietary guidelines on good fats in cardiovascular disease.

Omega-3 and omega-6 are essential fatty acids and must be supplied to us by diet. Omega-3 fatty acids have well-known biologic effects, which I listed in Table 1 in my article (this table includes only the cardiovascular effects; there are many others).[3] These are ignored in the review by Hooper et al.[1]

An outstanding systematic review (which included 97 studies and 275 000 patients) on various lipid-lowering agents and diets has concluded that omega-3 fatty acids are more effective than statins in reducing overall mortality and cardiac mortality.[4]

Most of the studies used in the *BMJ* review do not address the omega-6–to–omega-3 ratio. There is evidence that a 4:1 ratio is required for maximum benefit for cardiovascular disease and less than 2:1 to have any effect on cancer. This is almost impossible to achieve with our diet today (Canadian guidelines are currently 6:1). An excellent book, *Omega-6/Omega-3 Essential Fatty Acid Ratio: The Scientific Evidence,* reviews this.[5]

Confounders in the *BMJ* meta-analysis include the influence of the omega-6–to–omega-3 ratio; the pre-existing omega-3 status in the participants (if you

already have a full gas tank, adding more is not going to help your car); the source and type of omega-3; the strength and quality of the preparations; toxicants in the preparations; toxicant levels in people receiving omega-3 supplementation; and the design of each of the various studies used in the review. This is typical in the literature where one report shows one thing and another report (which neglects to address various confounders) shows another.

The main point of my article is that our ratio is much too high in (proinflammatory) omega-6 fatty acids and that advice to increase omega-3 fatty acids in the diet is needed. I did not address cancer, as the article was about cardiovascular effects, and this would have taken up more space than I was allowed.

I am quite concerned with the source and quality of omega-3 fatty acids, because these molecules are prone to oxidation and contamination. This is especially worrisome, as cardiovascular disease actually begins early in life (possibly in the perinatal period).[6] Lifetime ingestion might mean more exposure to contaminants. Also, oxidized fatty acids are dangerous to our health. Lipid peroxidation and oxidative stress are also important factors.

After reviewing the world literature, most researchers (I include myself) remain convinced that an abundance of research supports the recommendation to supply more omega-3 in the diet. I hope this is helpful in clarifying this interesting and hotly debated area of medicine.

I would also like to thank Dr Daniels for his excellent question on omega-3 and alpha-linolenic acid (ALA) and a possible link to prostate cancer. How can we advise patients to increase their intake of ALA for its cardioprotective benefit when we put men at greater risk of prostate cancer? This concern was raised in the June issue of *Patient Care*.[7]

An excellent review of ALA and prostate cancer is in a little book called *Flax—A Health and Nutrition Primer*[8] published by the Flax Council of Canada (**www.flaxcouncil.ca**). This lists 6 case-control studies and 2 cohort studies where some, but not all, show an increased risk of prostate cancer. The confounder in these studies (which usually use a food-frequency questionnaire) is that red meat is considered a source of ALA. Red meat has a very small amount of ALA; I did not include this in the list of sources of omega-3 fatty acids in my article. The Health Professionals Follow-up Study, cited in the *Patient Care* article,[7] has shown a link between red meat consumption and prostate cancer. If you consider red meat a source of ALA, I think you can understand how they have come to the conclusion that ALA is linked to prostate cancer. In the same study, ALA from plant sources was not linked to prostate cancer.

Personally I do not think there is a link with plant sources of ALA and prostate cancer, but well designed studies need to be done. There are many unanswered questions.

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